

Differences in cannabis-related experiences between patients with a first episode of psychosis and controls

F. Bianconi¹, M. Bonomo^{1*}, A. Marconi², A. Kolliakou³, S. A. Stilo¹, C. Iyegbe¹, P. Gurillo Muñoz⁴, S. Homayoun¹, V. Mondelli¹, S. Luzi¹, P. Dazzan¹, D. Prata^{5,6}, C. La Cascia⁷, J. O'Connor¹, A. David¹, C. Morgan¹, R. M. Murray¹, M. Lynskey⁸ and M. Di Forti¹

¹Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

²Department of Paediatrics and Child and Adolescent Neuropsychiatry, 'Sapienza' University of Rome, Rome, Italy

³Biomedical Research Centre Nucleus, King's College London, London, UK

⁴Hospital Marina Baixa, Alicante, Spain

⁵Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

⁶Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

⁷Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, Palermo, Italy

⁸Addiction Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

Background. Many studies have reported that cannabis use increases the risk of a first episode of psychosis (FEP). However, only a few studies have investigated the nature of cannabis-related experiences in FEP patients, and none has examined whether these experiences are similar in FEP and general populations. The aim of this study was to explore differences in self-reported cannabis experiences between FEP and non-psychotic populations.

Method. A total of 252 subjects, who met International Classification of Diseases (ICD)-10 criteria for FEP, and 217 controls who reported cannabis use were selected from the Genetics and Psychosis (GAP) study. The Medical Research Council Social Schedule and the Cannabis Experience Questionnaire were used to collect sociodemographic data and cannabis use information, respectively.

Results. Both 'bad' and 'enjoyable' experiences were more commonly reported by FEP subjects than controls. Principal components factor analysis identified four components which explained 62.3% of the variance. Linear regression analysis on the whole sample showed that the type of cannabis used and beliefs about the effect of cannabis on health all contributed to determining the intensity and frequency of experiences. Linear regression analysis on FEP subjects showed that the duration of cannabis use and amount of money spent on cannabis were strongly related to the intensity and frequency of enjoyable experiences in this population.

Conclusions. These results suggest a higher sensitivity to cannabis effects among people who have suffered their first psychotic episode; this hypersensitivity results in them reporting both more 'bad' and 'enjoyable' experiences. The greater enjoyment experienced may provide an explanation of why FEP patients are more likely to use cannabis and to continue to use it despite experiencing an exacerbation of their psychotic symptoms.

Received 6 May 2015; Revised 13 October 2015; Accepted 27 October 2015

Key words: Cannabis, Cannabis Experience Questionnaire, experiences, first episode of psychosis, psychosis.

Introduction

Cannabis is the most commonly used illicit drug internationally (United Nations Office on Drugs and Crime, 2014), and there is a current move in a number of countries to decriminalize or legalize its use. Previous studies in non-psychotic populations (Kendler & Prescott, 1998; Kendler *et al.* 2000, 2015) highlight that a

combination of genetic and environmental factors influence cannabis use. Patients with psychosis are more likely to use cannabis than the general population (D'Souza, 2007) but psychosis-prone individuals are not more likely to use cannabis (Henquet *et al.* 2005). Although cannabis use is widely recognized both as increasing risk for the development of psychosis and for exacerbating the course of psychotic illness (Henquet *et al.* 2005; D'Souza, 2007; Giordano *et al.* 2015), the processes through which cannabis has these effects remain largely unknown. Several theoretical models have been proposed. The indicator variable model hypothesizes that there are other factors that

* Address for correspondence: M. Bonomo, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.
(Email: matteo.bonomo@kcl.ac.uk)

cause both psychosis proneness and cannabis use (D'Souza *et al.* 2009). The self-medication hypothesis (Khantzian, 1985) posits that the intoxicating effects of cannabis (and other drugs) relieve both positive and negative symptoms of psychosis and that, therefore, people experiencing psychosis are more likely to use, and continue to use, cannabis; nevertheless this has not been supported by empirical studies (Kolliakou *et al.* 2015). Lastly, there is the causal model, which proposes that the risk of developing psychosis is increased by the use of cannabis. It points out that even though the majority of cannabis users will not develop psychotic symptomatology, cannabis use is associated with an increased risk of later psychotic experiences (Henquet *et al.* 2008; Casadio *et al.* 2011), while continued cannabis use is associated with poorer outcomes among individuals with psychosis (Zammit *et al.* 2008; van der Meer *et al.* 2015).

The causal model has attracted most support in recent years. However, it leaves an important question unanswered: 'why do patients with psychosis use or continue to use the drug if it makes them worse?' Indeed, the exact reasons why patients with psychosis use cannabis remain unclear. There has been little empirical research examining whether the subjective effects of cannabis differ between individuals with psychosis and members of the general population. This has been investigated, for the first time, in the present study. If psychosis is associated with a greater reactivity to, and enjoyment of, the effects of cannabis this might help explain the continued use of cannabis among those diagnosed with psychosis, despite evidence that such use may exacerbate their illness. In support of this, subjective pleasant experiences in the early stage of cannabis use predict later risks of cannabis dependence (Fergusson *et al.* 2003) and, furthermore, seem to be influenced by genetic factors (Lyons *et al.* 1997).

In testing any of the above models, cannabis potency needs to be addressed. In recent years, alongside traditional marijuana (grass) and resin (hash), a new potent variant (often termed skunk) has become widely available in many countries. Potter *et al.* (2009) reported skunk-type cannabis seized in 2005 in England to have an average Δ^9 -tetrahydrocannabinol (Δ^9 -THC) content of 12.9% compared with an average 3.6% of hash-type cannabis, while the UK Home Office (Mwenda *et al.* 2005) reported a slight increase in the average content of Δ^9 -THC for both types: 16.2% in skunk and 5% in hash. Both potency studies also reported that cannabidiol levels were almost absent in high-potency skunk-like cannabis (0.1%).

A second aspect to consider closely is that genetic susceptibility may also render some individuals more vulnerable to cannabis-related psychosis. In particular, as

we and others have shown, carriers of the C allele of *AKT1* rs2494732, which is involved in dopamine signalling, have an increased risk of psychosis onset after cannabis use (van Winkel *et al.* 2011; Di Forti *et al.* 2012, 2015).

We set out to compare the self-reported effects of cannabis between first-episode psychosis patients and matched controls from the general population, and to take into account the type of cannabis used as well as frequency of use.

Method

Sample

This study utilized a subsample of the Genetic and Psychosis (GAP) sample (Di Forti *et al.* 2009) and comprised 252 patients who met International Classification of Diseases (ICD)-10 (World Health Organization, 1992) criteria for a first episode of psychosis (FEP), and 217 controls, all of whom reported using cannabis. The patients were aged 18–65 and presented with a FEP to the Lambeth, Southwark and Croydon adult in-patient units of the South London and Maudsley (SLaM) NHS Foundation Trust, between 1 May 2005 and 31 May 2011. In addition to ICD-10, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing *et al.* 1990) were used to clarify symptomatology during the month before the assessment. Patients who met the diagnostic criteria for organic psychosis (ICD-10, F09) were excluded from the cohort. The control group was recruited from the same area of South-East London; those who met criteria for a psychotic disorder or with a previous diagnosis of psychotic illness were excluded (Di Forti *et al.* 2009).

Measures

We collected sociodemographic data (age, gender; self-reported ethnicity) through the Medical Research Council Social Schedule (MRCSS). From March 2006, we collected more detailed history of cannabis use by adding the Cannabis Experience Questionnaire modified version (CEQ_{mv}; Di Forti *et al.* 2009); this included frequency of use and type of cannabis used, age of first use, if they still use, frequency of this current use and the use of other substances. We investigated experiences reported both during and after cannabis intoxication, which were collected with a five-point Likert scale (from rarely or never to always) and a subjective rating of the quality of that experience ('good', 'bad' or 'neutral'). Contrary to the original version of the CEQ (Barkus *et al.* 2006), which included 55 experiences, the CEQ_{mv} (Di Forti *et al.* 2009) includes only 14 items to reduce respondent burden (which was selected following factor analyses; Table 2).

All participants were also asked to describe the type of cannabis they typically used, and divided into two categories: hash-type (median THC: 3.54%) and skunk-type (median THC: 13.98%); according to features of cannabis samples seized by the Metropolitan Police in South-East London and the later UK Home Office Study (Hardwick & King, 2008; Potter *et al.* 2009), grass-type cannabis is rarely used in this area and less than 1% of participants used it. In our study those using imported herbal cannabis were included in the high-potency category due to the high level of THC contained (Potter *et al.* 2009).

Statistical analysis

The χ^2 test was used to compare cannabis-related experiences in patients and controls and Pearson correlations to investigate the relationship between the experiences, and the frequency, the type of cannabis use and the genetic vulnerability to psychosis symptomatology. Principal component analysis with Varimax rotation was run in order to create variables able to summarize the areas involved in cannabis intoxication and understand if these cannabis-related experiences could have any role in the maintenance of cannabis use.

The components obtained with the principal component analysis were analysed using multiple linear regression to understand the relationship between experiences and environmental/personal variables. For each factor a score was calculated using the factor loadings and this formed the dependent variable in linear regression analyses. Independent variables included: the 'will to stop using cannabis', the 'amount of money spent per week on cannabis', the 'duration of cannabis use' and the 'current status (as current user or not)', the 'frequency of cannabis use', the 'type of cannabis mostly used', the 'age at first cannabis use', the 'presence of positive family history for psychosis or for other psychiatric disorders' and the 'beliefs about the impact of cannabis use on health'. 'Caseness' (presence of diagnosis of a psychotic disorder) was forced as an independent variable for all the analyses.

To account for multiple comparisons we used Bonferroni correction (on the basis of the number of predictors included) and only p values lower than 0.006 were considered significant.

Results

A total of 252 patients [74.6% male; mean age 28 (s.d. = 8.32) years] and 217 controls [57.4% male; mean age 30 (s.d. = 9.49) years] were included in the analysis. Of the FEP participants, 22.8% were employed at the time of the interview compared with 61.0% of controls;

18.8% of patients had no education qualification as opposed to 2.5% of the controls. The duration of cannabis use did not differ between the two groups. However, high-potency skunk-like cannabis was more commonly used by FEP patients (83.7%) than controls (44.4%) (Table 1).

Cannabis-related experiences

The experiences were divided into two categories: (a) experiences during cannabis intoxication; and (b) experiences after the effect of cannabis had worn off. Both categories showed significant differences between patients and controls (Table 2). For experiences 'during' cannabis use, feeling like going mad ($\chi^2 = 13.729$, $p = 0.001$), feeling nervous ($\chi^2 = 12.287$, $p = 0.002$), feeling suspicious without a reason ($\chi^2 = 9.556$, $p = 0.002$), feeling happy ($\chi^2 = 10.439$, $p = 0.005$), feeling full of plans ($\chi^2 = 8.544$, $p = 0.014$) and hearing voices ($\chi^2 = 10.644$, $p = 0.005$) were more common within FEP participants than controls.

Additionally, some experiences 'after' cannabis use were more frequently noted by patients than controls: being suspicious without a reason ($\chi^2 = 6.737$, $p = 0.034$) and difficulty concentrating ($\chi^2 = 13.496$, $p = 0.001$).

Principal component analysis

A Principal component analysis with Varimax rotation of the 13 cannabis experiences (Table 3) identified four factors (eigenvalues between 1.183 and 4.575) which overall explained 62.3% of the total variance in cannabis-related experiences. Each of the four factors was retained in subsequent analyses as each explained more than 10% of the total variance. The factor loadings and item-total correlations for this four-factor solution are summarized in Table 3.

The first factor component was defined by four items each with a factor loading >0.5 , and explained 21.0% of the total variance. Even though the item 'how often have you felt suspicious without a reason after effects of cannabis have worn off?' showed a higher factor loading for another component as well, we considered it part of this component to preserve its coherence. This component had good internal consistency (Cronbach's $\alpha = 0.78$) and the items showed acceptable item-total correlations. The items included in this factor related to anxiety, fear and suspicion and therefore this factor was labelled as 'anxiety-paranoid'.

The second factor component consisted of three items with each factor loading >0.5 and explained 16.09% of the total variance; this component also displayed good internal consistency (Cronbach's $\alpha = 0.77$) and the items, which form it, showed good item-total correlation. The items comprising this factor

Table 1. Sociodemographic characteristics and patterns of cannabis use in cases and controls

	Cases (n = 252)	Controls (n = 217)	χ^2 (df)
Mean age, years (s.d.)	28 (8.32)	30 (9.49)	
Gender, n (%)			<0.001 (1)
Male	188 (74.6)	124 (57.4)	
Female	64 (25.4)	92 (42.6)	
Ethnicity, n (%)			<0.001(3)
White	102 (40.5)	144 (67.9)	
Black Caribbean	41 (16.3)	27 (12.7)	
Black African	45 (17.9)	14 (6.6)	
Other	64 (25.4)	27 (12.7)	
Employment, n (%)			<0.001 (2)
Employed	43 (22.8)	94 (61.0)	
Student	16 (8.5)	36 (23.4)	
Unemployed	130 (68.8)	24 (15.6)	
Education, n (%)			<0.001 (1)
No qualification	36 (18.8)	4 (2.5)	
Any qualification	155 (81.2)	153 (97.5)	
Mean age of first cannabis use, years (s.d.)	16 (4.77)	17 (3.33)	
Mean duration of cannabis use, years (s.d.)	9.63 (9.13)	9.62 (8.89)	
Type of cannabis used, n (%)			<0.001 (1)
Skunk type	159 (83.7)	63 (44.4)	
Hash type	31 (16.3)	79 (55.6)	
Other drugs lifetime use, n (%)			>0.05 (1)
No	88 (40.0)	82 (44.6)	
Yes	132 (60.0)	102 (55.4)	
Tobacco lifetime use, n (%)			<0.001 (1)
No	18 (8.1)	71 (34.8)	
Yes	205 (91.9)	133 (65.2)	
Alcohol use, n (%)			>0.05 (1)
<14 units per week	67 (65.0)	111 (68.9)	
>14 units per week	36 (35.0)	50 (31.1)	

df, Degrees of freedom; s.d., standard deviation.

related to thought and concentration and we therefore labelled this factor 'cognitive experiences'.

The third factor component, which we called 'enjoyable experiences' due to all the pleasant experiences included, showed acceptable Cronbach's α values (0.63) and item-total correlations. This component explained 13.1% of the total variance.

The final factor component was characterized by the presence of positive symptoms and we labelled it 'psychotic experiences'. This explained 12.2% of the total variance, had a lower internal consistency index

(Cronbach's $\alpha = 0.58$) but its items displayed an acceptable level of item-total correlation.

Linear regression

The best-fitting models (Table 4) showed that belief about the impact of cannabis on health was one of the strongest predictors of unpleasant experiences, suggesting that cannabis users are able to identify adverse effects of cannabis. However, awareness of the adverse effects of cannabis was not associated with a stronger motivation to stop using cannabis. Investigating the whole-sample 'enjoyable experiences' did not show any strong association with the considered independent variables; considering only the FEP subgroup, this factor was positively related to the amount of money spent weekly on cannabis as well as to a longer duration of cannabis use (Table 5), suggesting that these positive experiences reinforce further cannabis use in psychotic patients.

Use of high-potency cannabis was related to more frequent psychotic experiences, indicating that use of skunk instead of hash increased psychotic symptomatology.

To better understand the relationship between psychotic illnesses and sensitivity to the effects of cannabis, we tested for significant interactions between caseness and each of the significant predictors. None of these interactions was significant, suggesting that the associations between predictors and cannabis-related experiences did not differ between patients and controls.

No multilinearity problems were found between the considered predictors.

Discussion

In line with our previous reports, the FEP subjects in our sample, relative to controls, were more likely to use cannabis frequently, preferred potent varieties (Di Forti *et al.* 2009, 2015; Kolliakou *et al.* 2011) and reported an earlier age of onset of cannabis use (Di Forti *et al.* 2014). Although there were no significant differences in the duration of cannabis use between the two groups, at the time of the interviews, more patients than controls had been currently smoking cannabis.

We show that FEP patients showed higher sensitivity to cannabis than controls as also reported in other studies (Radhakrishnan *et al.* 2014). This hypersensitivity involved not only more frequent 'unpleasant experiences' but also increased 'enjoyable feelings'. These intensified enjoyable experiences could reinforce, working as a reward, cannabis use (Wetherill *et al.* 2014) in both patients and controls, increasing the risk of developing cannabis dependence and balancing, at the same time, the experience of unpleasant effects.

Table 2. Cannabis experiences in patients v. controls

		Patients, <i>n</i> (%) (<i>n</i> = 252)	Controls, <i>n</i> (%) (<i>n</i> = 217)	χ^2	<i>p</i> (df = 2)
How often have you felt fearful while smoking cannabis?	Rarely or never	125 (65.4)	86 (66.2)	2.433	0.296
	From time to time	15 (7.9)	16 (12.3)		
	Sometimes, more often than not, almost always	51 (26.7)	28 (21.5)		
How often have you felt mad while smoking cannabis?	Rarely or never	134 (70.2)	107 (82.3)	13.729	0.001
	From time to time	9 (4.7)	11 (8.5)		
	Sometimes, more often than not, almost always	48 (25.1)	12 (9.2)		
How often have you felt nervy while smoking cannabis?	Rarely or never	102 (53.7)	80 (61.5)	12.278	0.002
	From time to time	20 (10.5)	25 (19.2)		
	Sometimes, more often than not, almost always	68 (35.8)	25 (19.2)		
How often have you felt suspicious while smoking cannabis?	Rarely or never	100 (53.2)	70 (53.8)	9.556	0.008
	From time to time	14 (7.4)	23 (17.7)		
	Sometimes, more often than not, almost always	74 (39.4)	37 (28.5)		
How often have you felt happy while smoking cannabis?	Rarely or never	37 (19.3)	17 (13.1)	10.439	0.005
	From time to time	11 (5.7)	21 (16.2)		
	Sometimes, more often than not, almost always	144 (75.0)	92 (70.8)		
How often have you felt full of plans while smoking cannabis?	Rarely or never	66 (35.1)	58 (45.0)	8.544	0.014
	From time to time	16 (8.5)	19 (14.7)		
	Sometimes, more often than not, almost always	106 (56.4)	52 (40.3)		
How often have you heard voices while smoking cannabis?	Rarely or never	143 (75.7)	116 (89.9)	10.644	0.005
	From time to time	10 (5.3)	4 (3.1)		
	Sometimes, more often than not, almost always	36 (19.0)	9 (7.0)		
How often have you felt able to understand the world better while smoking cannabis?	Rarely or never	93 (49.7)	71 (54.6)	5.471	0.065
	From time to time	11 (5.9)	15 (11.5)		
	Sometimes, more often than not, almost always	83 (44.4)	44 (33.8)		
How often have you had visions while smoking cannabis?	Rarely or never	161 (85.2)	112 (86.8)	1.808	0.405
	From time to time	10 (5.3)	3 (2.3)		
	Sometimes, more often than not, almost always	18 (9.5)	14 (10.9)		
How often have you felt not wanting to do anything after effects of cannabis have worn off?	Rarely or never	78 (43.6)	45 (40.5)	1.153	0.562
	From time to time	13 (7.3)	12 (10.8)		
	Sometimes, more often than not, almost always	88 (49.2)	54 (48.6)		
How often have you felt suspicious without a reason after effects of cannabis have worn off?	Rarely or never	109 (61.2)	82 (74.5)	6.737	0.034
	From time to time	14 (7.9)	9 (8.2)		
	Sometimes, more often than not, almost always	55 (30.9)	19 (17.3)		
How often have you felt your thinking was slowed down after effects of cannabis have worn off?	Rarely or never	92 (51.7)	51 (45.9)	5.796	0.055
	From time to time	14 (7.9)	19 (17.1)		
	Sometimes, more often than not, almost always	72 (40.4)	41 (36.9)		
How often have you had difficulty concentrating after effects of cannabis have worn off?	Rarely or never	86 (48.6)	52 (46.8)	13.496	0.001
	From time to time	12 (6.8)	23 (20.7)		
	Sometimes, more often than not, almost always	79 (44.6)	36 (32.4)		

df, Degrees of freedom.

Table 3. *Principal component analysis of cannabis-related experiences*

	Factor 1 'anxiety-paranoid experiences'		Factor 2 'cognitive experiences'		Factor 3 'enjoyable experiences'		Factor 4 'psychotic experiences'	
	Factor loading	Item-total correlation	Factor loading	Item-total correlation	Factor loading	Item-total correlation	Factor loading	Item-total correlation
How often have you felt suspicious while smoking cannabis?	0.776	0.574						
How often have you felt nervy while smoking cannabis?	0.760	0.567						
How often have you felt fearful while smoking cannabis	0.701	0.558						
How often have you felt suspicious without a reason after effects of cannabis have worn off?	0.591	0.554						
How often have you felt your thinking was slowed down after effects of cannabis have worn off?			0.796	0.624				
How often have you had difficulty concentrating after effects of cannabis have worn off?			0.787	0.615				
How often have you felt not wanting to do anything after effects of cannabis have worn off?			0.717	0.559				
How often have you felt able to understand the world better while smoking cannabis?					0.741	0.424		
How often have you felt full of plans while smoking cannabis?					0.730	0.510		
How often have you felt happy while smoking cannabis?					0.705	0.388		
How often have you had visions while smoking cannabis?							0.765	0.355
How often have you heard voices while smoking cannabis?							0.677	0.472
How often have you felt like going mad while smoking cannabis?							0.588	0.522
% Variance explained		21.0		16.1		13.1		12.2
Cronbach's α		0.78		0.77		0.63		0.58

Table 4. Linear regression analysis aspects of cannabis use and belief about the health effects of cannabis on subjective experiences of cannabis use^a

	Anxiety-paranoid experiences		Cognitive experiences		Psychotic experiences		Enjoyable experiences	
	B	p	B	p	B	p	B	p
Caseness	−0.042 (0.24)	0.86	−0.35 (0.31)	0.26	0.23 (0.16)	0.143	−0.07 (0.174)	0.69
Type of cannabis used					1.03 (0.34)	<0.01**		
Belief about the effect of cannabis on health	2.11 (0.38)	<0.001***	1.52 (0.49)	<0.01**	0.96 (0.27)	<0.001***		
R ²	0.421		0.183		0.264			
p	<0.001***		<0.01**		<0.001***			

Data are given as regression coefficient (standard error).

^a Predictors which did not show significant results with the dependent variables are not reported in this table: alcohol use; other drugs use; tobacco use; amount of money spent on cannabis; duration of cannabis use; frequency of cannabis use. Confounder variables: age, gender and ethnicity.

** $p < 0.01$, *** $p < 0.001$.

We found that a larger amount of money spent per week was positively associated with enjoyable experiences in the patient group whereas unpleasant experiences were positively associated with the presence of beliefs about the impact of cannabis use on health; thus, FEP patients were aware of the unhealthy effect of cannabis on them.

We demonstrate that psychotic patients are more susceptible to all the psychological effects of cannabis, not only the positive ones as shown in previous literature (Thornton *et al.* 2012). Happiness and fluency of thinking were more often reported by patients than controls and were positively associated with a larger amount of money spent per week to purchase the substance. It is likely that these positive cannabis-related experiences may contribute to the persistence of cannabis use in psychotic patients, consistent with previous findings (Zeiger *et al.* 2012).

The significant association between more frequent cannabis-related psychotic experiences and the potent variant of cannabis is in line with the association between the use of skunk and higher risk of psychosis which we previously found (Di Forti *et al.* 2015).

Why are psychotic patients more sensitive to cannabis? One possibility is that they become more sensitive following the onset of psychosis. An alternative explanation is that they already held an intrinsic sensitivity. For instance, evidence has suggested a role of variation in the *AKT1* gene in influencing the individual response to the psychotogenic properties of cannabis use (van Winkel *et al.* 2011; Di Forti *et al.* 2012, 2015). The *AKT1* gene encodes for a kinase protein involved in post-synaptic D₂ dopamine signalling and to post-synaptic sensitivity and it has

been suggested to moderate the risk for psychosis (Murray *et al.* 2014).

These results should be considered in the light of some limitations and strengths; first of all the large number of missing data; 61.4% of our sample completed all questions about the experiences included in the CEQ with a range of missing data between 31.3 and 38.6%; as reported earlier a large proportion of those missing data was related to the later introduction of the CEQ_{mv} in the collection of cannabis history; a higher presence of missing data was also observed within the control group, especially for those who had used cannabis once.

In conclusion, our findings highlight the hypersensitivity of FEP patients to the effects of cannabis; this hypersensitivity was linked to stronger experiences not only during intoxication, but also to cognitive impairment after cannabis use and these, as well as other experiences, were also related to genetic susceptibility. Contrary to the self-medication hypothesis, cannabis did not relieve psychotic symptomatology as higher levels of psychotic experiences were reported by FEP patients. It seems that other factors, including pleasure seeking, may encourage and maintain cannabis use in FEP patients. The relationship between the type of cannabis use and a massive presence of psychotic experiences support the causal model, highlighting the presence of a third factor which increases the risk to have psychotic-related experiences after cannabis use.

Our findings concerning both skunk use and more enjoyable experiences reported during cannabis intoxication are in line with the indicator variable model showing how different factors can guide the relationship between psychosis-proneness and cannabis use.

Table 5. Linear regression analysis aspects of cannabis use on subjective experiences of cannabis use (FEP group)^a

	Anxiety–paranoid experiences		Cognitive experiences		Psychotic experiences		Enjoyable experiences	
	B	p	B	p	B	p	B	p
Duration of cannabis use							0.79 (0.24)	<0.01**
Amount of money spent on cannabis							0.40 (0.09)	<0.001***
R ²							0.349	
p							<0.001***	

Data are given as regression coefficient (standard error).

FEP, First episode of psychosis.

^a Predictors which did not show significant results with the dependent variables are not reported in this table: Alcohol use, other drugs use, tobacco use, beliefs about the effect of cannabis on health, type of cannabis use, frequency of cannabis use. Confounder variables: age, gender and ethnicity.

** $p < 0.01$, *** $p < 0.001$.

Because our data were collected from a FEP population and the cannabis-related experiences included experiences occurring both before and after the onset of psychosis, further prospective studies should assess the changes in subjective cannabis experiences before and after the exacerbation of psychosis considering also if antipsychotic medication could change the subjective cannabis-related experience playing a role in the maintenance of cannabis use. The role of individual genetic variants and/or polygenic risk score for psychosis should be explored to understand their role in influencing the quality and frequency of cannabis-related experience and the maintenance of cannabis use.

Acknowledgements

The study was funded by the UK National Institute of Health Research (NIHR) Specialist Biomedical Research Centre for Mental Health, the South London and Maudsley (SLaM) NHS Foundation, the Institute of Psychiatry of King's College London, the Psychiatry Research Trust, Maudsley Charity Research Fund, and the European Community's Seventh Framework Programme (grant agreement no. HEALTH-F2-2009-241909; project EU-GEI). The study was supported by the Genetics and Psychosis (GAP) and Physical Health and Substance Use Measures in First Onset Psychosis (PUMP) study teams of the Institute of Psychiatry, King's College London, and SLaM.

Declaration of Interest

None.

References

- Barkus EJ, Stirling J, Hopkins RS, Lewis S (2006). Cannabis-induced psychosis-like experiences are associated with high schizotypy. *Psychopathology* **39**, 175–178.
- Casadio P, Fernandes C, Murray RM, Di Forti M (2011). Cannabis use in young people: the risk for schizophrenia. *Neuroscience and Biobehavioral Reviews* **35**, 1779–1787.
- Di Forti M, Iyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, Sirianni M, La Cascia C, Stilo SA, Marques TR, Handley R, Mondelli V, Dazzan P, Pariente C, David AS, Morgan C, Powell J, Murray RM (2012). Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biological Psychiatry* **72**, 811–816.
- Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, Bianconi F, Gardner-Sood P, O'Connor J, Russo M, Stilo SA, Marques TR, Mondelli V, Dazzan P, Pariente C, David AS, Gaughran F, Atakan Z, Iyegbe C, Powell J, Morgan C, Lynskey M, Murray RM (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry* **2**, 233–238.
- Di Forti M, Morgan C, Dazzan P, Pariente C, Mondelli V, Marques TR, Handley R, Luzzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B, Powell J, Murray RM (2009). High-potency cannabis and the risk of psychosis. *British Journal of Psychiatry* **195**, 488–491.
- Di Forti M, Sallis H, Allegrì F, Trotta A, Ferraro L, Stilo SA, Marconi A, La Cascia C, Reis Marques T, Pariente C, Dazzan P, Mondelli V, Paparelli A, Kolliakou A, Prata D, Gaughran F, David AS, Morgan C, Stahl D, Khondoker M, MacCabe JH, Murray RM (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin* **40**, 1509–1517.
- D'Souza DC (2007). Cannabinoids and psychosis. *International Review of Neurobiology* **78**, 289–326.

- D'Souza DC, Sewell RA, Ranganathan M (2009). Cannabis and psychosis/schizophrenia: human studies. *European Archives of Psychiatry and Clinical Neuroscience* **259**, 413–431.
- Fergusson DM, Horwood LJ, Swain-Campbell NR (2003). Cannabis dependence and psychotic symptoms in young people. *Psychological Medicine* **33**, 15–21.
- Giordano GN, Ohlsson H, Sundquist K, Sundquist J, Kendler KS (2015). The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study. *Psychological Medicine* **45**, 407–414.
- Hardwick S, King L (2008). *Home Office Cannabis Potency Study 2008*. Home Office Scientific Development Branch: London.
- Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM (2008) Gene–environment interplay between cannabis and psychosis. *Schizophrenia Bulletin* **34**, 1111–1121.
- Henquet C, Murray RM, Linszen D, van Os J (2005). The environment and schizophrenia: the role of cannabis use. *Schizophrenia Bulletin* **31**, 608–612.
- Kendler KS, Karkowski LM, Neale MC, Prescott CA (2000). Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Archives of General Psychiatry* **57**, 261–269.
- Kendler KS, Ohlsson H, Maes HH, Sundquist K, Lichtenstein P, Sundquist J (2015). A population-based Swedish Twin and Sibling Study of cannabis, stimulant and sedative abuse in men. *Drug and Alcohol Dependence* **149**, 49–54.
- Kendler KS, Prescott CA (1998). Cannabis use, abuse, and dependence in a population-based sample of female twins. *American Journal of Psychiatry* **155**, 1016–1022.
- Khantzian EJ (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *American Journal of Psychiatry* **142**, 1259–1264.
- Kolliakou A, Castle D, Sallis H, Joseph C, O'Connor J, Wiffen B, Ismail K (2015). Reasons for cannabis use in first-episode psychosis: does strength of endorsement change over 12 months? *European Psychiatry* **30**, 152–159.
- Kolliakou A, Joseph C, Ismail K, Atakan Z, Murray RM (2011). Why do patients with psychosis use cannabis and are they ready to change their use? *International Journal of Developmental Neuroscience* **29**, 335–346.
- Lyons MJ, Toomey R, Meyer JM, Green AI, Eisen SA, Goldberg J, True WR, Tsuang MT (1997). How do genes influence marijuana use? The role of subjective effects. *Addiction* **92**, 409–417.
- Murray RM, Mehta M, Di Forti M (2014). Different dopaminergic abnormalities underlie cannabis dependence and cannabis-induced psychosis. *Biological Psychiatry* **75**, 430–431.
- Mwenda L, Ahmad M, Kumari K (2005). *Seizures on Drugs in England and Wales, 2003. Findings 265*. Home Office Research, Development and Statistics Directorate. Office for National Statistics: London.
- Potter DJ, Clark P, Brown MB (2009). Potency of Δ^9 -THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. *Journal of Forensic Science* **53**, 90–94.
- Radhakrishnan R, Wilkinson ST, D'Souza DC (2014). Gone to pot – a review of the association between cannabis and psychosis. *Frontiers in Psychiatry* **5**, 54.
- Thornton LK, Baker AL, Johnson MP, Kay-Lambkin F, Lewin TJ (2012). Reasons for substance use among people with psychotic disorders: method triangulation approach. *Psychology of Addictive Behaviors* **26**, 279–288.
- United Nations Office on Drugs and Crime (2014). *World Drug Report 2014*. United Nations publication, sales no. E.14.XL7. United Nations: New York.
- van der Meer FJ, Velthorst E; Genetic Risk and Outcome of Psychosis (GROUP) Investigators (2015). Course of cannabis use and clinical outcome in patients with non-affective psychosis: a 3-year follow-up study. *Psychological Medicine* **45**, 1977–1988.
- van Winkel R, van Beveren NJM, Simons C; Genetic Risk and Outcome of Psychosis (GROUP) Investigators (2011). AKT1 moderation of cannabis-induced cognitive alterations in psychotic disorder. *Neuropsychopharmacology* **36**, 2529–2537.
- Wetherill RR, Childress AR, Jagannathan K, Bender J, Young KA, Suh JJ, O'Brien CP, Franklin TR (2014). Neural responses to subliminally presented cannabis and other emotionally evocative cues in cannabis-dependent individuals. *Psychopharmacology (Berlin)* **231**, 1397–1407.
- Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N (1990). SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Archives of General Psychiatry* **47**, 589–593.
- World Health Organization (1992) *ICD-10 Classifications of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva.
- Zammit S, Moore TH, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2008). Effects of cannabis use on outcomes of psychotic disorders: systematic review. *British Journal of Psychiatry* **193**, 357–363.
- Zeiger JS, Haberstick BC, Corley RP, Ehringer MA, Crowley TJ, Hewitt JK, Hopfer CJ, Stallings MC, Young SE, Rhee SH (2012). Subjective effects for alcohol, tobacco, and marijuana association with cross-drug outcomes. *Drug and Alcohol Dependence* **123** (Suppl. 1), S52–S58.